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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,142	10/09/2003	J. Michael Ramstack	000166.0073-US02	6453

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EXAMINER	
TRAN, SUSAN T	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,142	RAMSTACK ET AL.	
	Examiner	Art Unit	
	Susan T. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/06/07 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11 and 13-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. While the present specification at page 20 and 26 disclose the microparticles are suspended at a concentration of about 100 mg/ml to about 400 mg/ml, or preferably at a concentration of about 150 mg/ml to about 300 mg/ml, it appears that nowhere in the specification provides support for the limitation "from about 175 mg/ml" and "greater than about 300 mg/ml and less than

about 400 mg/ml". The specification does not provide adequate guidance to allow one of ordinary skill in the art to narrow the concentration from a broad range "100-400 mg/ml" down to "greater than 300 but less than 400 mg/ml". Page 19 of the present specification shows an increase in concentration from 175 mg/ml to 250 mg/ml to improve injectability. The specification again, does not fulfill the written description with respect to the concentration of the microparticles in the injection vehicle.

Claims 1-9, 11 and 13-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition suitable for injection through a needle into a host comprising dry microparticles suspended in an injection vehicle, does not reasonably provide enablement for the microparticles suspended in injection vehicle at a concentration of from about 175 mg/ml to about 400 mg/ml. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: breadth of the claims, nature of the invention, state of the prior art, amount of direction provided by the inventor, the level of predictability in the art, the existence of working examples, quantity of experimentation needed to make or use the invention based on the content of the disclosure, and relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors being discussed below:

Independent claims are directed to a composition suitable for injection through a needle into a host comprising dry microparticles suspended in an injection vehicle, wherein the microparticles are suspended in the injection vehicle at a concentration of from about 175 mg/ml to about 400 mg/ml.

Amount of direction provided by the inventor: the present specification discloses a concentration of greater than 30 mg/ml, preferably from about 100 mg/ml to about 400 mg/ml. The specification does not provide any guidance showing that the injectability of the composition through a needle ranging from 18-22 gauge can be achieved with the microparticles concentration as low as 175 mg/ml. As evident by the specification at page 19, 1st paragraph that increasing concentration from 175 mg/ml to 250 mg/ml improves the injectability. As such, the practitioner would turn to trial and error experimentation in order to compose a composition suitable for the injection through a needle ranging from 18-22 gauge without guidance from the specification or the prior art.

The relative skill of those in the art: the skill of those in the art is very high, *e.g.*, Ph.D. or M.D. level technology.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Claims 1-9, 11, 13 and 15-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francois et al. WO 97/44039, in view of Ramstack et al. WO 95/13799.

Francois teaches an aqueous suspension formulation comprising particles of 9-hydroxyrisperidone dispersed or suspended in a pharmaceutically acceptable carrier such as water (page 4, lines 21-30; and page 5, lines 34-37). The aqueous suspension further comprises a suspending agent and a wetting agent, such as sodium carboxymethyl cellulose (page 6, lines 1-17). The formulation is suitable for parenteral administration through fine needle ranging from 21-22 gauge (page 7, lines 1-5; and examples). Francois does not teach mixing the ingredients in the claimed order (see page 7, lines 19-29). However, selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930). See also Ex parte Rubin, 128 USPQ 440 (Bd. App. 1959). Accordingly, it would have been obvious to one of ordinary skill in the art to, by routine experimentation modify the order of mixing the ingredients to obtain the claimed invention, because Francois teaches the use of the same ingredients for the same purpose, namely, an efficient, well-tolerated injectable formulation of 9-hydroxyrisperidone, suitable for fine needle having diameter ranges from 21-22 gauge.

It is noted that Francois does not teach the viscosity of the suspending agent. However, it is the position of the examiner that the suspending agent taught by Francois would have the claimed viscosity, because Francois teaches the use of the same

suspending agent, *e.g.*, sodium carboxymethyl cellulose, to obtain the same composition, *e.g.*, an aqueous suspension suitable for injection through a needle into a host. Similarly, Francois does not teach the claimed concentration of the microparticles in the injection vehicle. However, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, one of ordinary skill in the art would have been motivated to, by routine experimentation determine a suitable microparticles concentration to obtain the claimed invention, because Francois teaches an injectionable composition useful for the claimed active agent, which provides injectability through a needle ranging in diameter falls within the claimed range, from 21-22 gauge.

Francois does not expressly teach the claimed polymeric binder.

Ramstack teaches a microparticles formulation suitable for parenteral administration comprising polymeric matrix including poly(d,l-lactic-co-glycolic acid) having a molar ratio from about 85:15 to about 50:50 (pages 15-16). The microparticles further comprises risperidone as active agent (page 30, lines 16-20; and examples). Thus, it would have been obvious to one of ordinary skill in the art to modify the formulation of Francois using the microparticles of risperidone in view of the teaching of Ramstack, because Ramstack teaches a biodegradable system, an injectable system that prevents the loss of dose during treatment, because Ramstack teaches

microparticles for controlled/sustained release of risperidone, because Ramstack teaches dry microparticles of risperidone are suspended in an acceptable pharmaceutical liquid vehicle prior to administration to a patient (page 29, lines 27-31), and because Francois teaches the desirability of obtaining an efficient, well-tolerated, sustained or delayed release injectable composition of a 9-hydroxyrisperidone (page 3, lines 23-26).

Francois further does not explicitly teach mixing the ingredients in a syringe, as claimed in claims 8, 9, 15 and 16.

Ramstack teaches microparticles were syringe loaded and resuspended in the syringe with an injection vehicle. The suspension was reconstituted with WFI prior to injection (page38, lines 4-9). Thus, it would have been obvious to one of ordinary skill in the art to use the syringe in view of the teaching of Ramstack to mix the ingredients taught by Francois, because Ramstack teaches a known method for mixing or reconstitute active agents with an injectable vehicle prior to administration to a patient.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Francois et al. WO 97/44039, in view of Ramstack et al. WO 95/13799 and Okada et al. US 5,631,021.

Francois and Ramstack are relied upon for the reasons stated above. Francois does not explicitly teach changing the temperature of the suspension.

Okada teaches procedures for increasing the viscosity include a heat treatment, cooling to a low temperature, freezing, changing pH, or adding carboxymethyl cellulose

(column 6, lines 16-24). Thus, it would have been obvious to one of ordinary skill in the art to change the temperature of the suspension to obtain a desirable injectable formulation in view of the teaching of Okada, because Okada teaches changing temperature to obtain a desirable viscosity is well known in the art, and because Okada teaches a known equivalent of changing the temperature and adding carboxymethyl cellulose.

Response to Arguments

Applicant's arguments filed 06/06/07 have been fully considered but they are not persuasive.

Applicant argues that none of the documents cited by the Examiner discloses explicitly or inherently a microparticle concentration range between 175 mg/ml and 400 mg/ml. Moreover, the claimed combination of high viscosity and high microparticle concentration is unexpected in light of the conventional teaching that an increase in viscosity and an increase in concentration of solids in suspension both hinder the syringeability of suspensions. As such, one skilled in the art would not expect the increased viscosity and concentration of the microparticles as claimed to provide injectability through a needle of 18-22 gauge, or more generally, through a needle of medically acceptable size.

However, as discussed in the 103(a) rejection above, Francois teaches an injection composition that provides injectability through needle having gauge size falls within the claimed range. As admitted by the applicant, it is known in pharmaceutical art

that an increase in viscosity and an increase in concentration of solids in suspension hinder the syringeability of the suspension (see applicant's remarks dated 06/06/07 at page 10, first paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art to, by routine experimentation determine a suitable microparticles concentration to obtain an injection composition that provides injectability through a needle of medically acceptable size.

Applicant argues that the rejections under § 103(a) cannot properly be maintained for the additional reason that the documents cannot properly be combined. As fully explained in the Amendment in Response to Non-Final Office Action dated December 5, 2006, there is no motivation to combine WO 97/44039 with WO 95/13799 because WO 97/44039 teaches away from use of risperidone itself, which is the active agent used in WO 95/13799, and there would be no reasonable expectation of success to substitute risperidone encapsulated in a biodegradable and biocompatible polymer for the crystalline form of the metabolite. Importantly, in attempting to explain why Applicants' arguments are not persuasive, the Examiner never directly addresses, much less refutes, the foregoing assertions. Rather, the Examiner merely recites three sentences of what the two documents allegedly teach (See, page 6 of the Final Office Action). Contrary to law and U.S. Patent and Trademark Office practice, the Examiner provides no reason why one skilled in the art would combine the teachings of the "Ramstack" (WO 95/13799) and "Francois" (WO 97/44039) documents. For at least this reason, Applicants respectfully submit that the § 103(a) rejections were not properly

made in the Final Office Action, and nor can they properly be maintained against the claims as presented herein.

Contrary to the applicant's argument, it is noted that applicant's arguments dated 12/05/06 have been fully considered and addressed in the final office action. The response is being repeated herein. In response to applicant's argument that there is no motivation to combine Ramstack and Francois because Francois teaches away from the use of risperidone itself, which is the active agent used in Ramstack, and there would be no reasonable expectation of success to substitute risperidone encapsulated in a biodegradable and biocompatible polymer for the crystalline form of the metabolite. However, it is noted that Ramstack was not cited for the teaching of the active agent, but cited solely for the teaching of the claimed polymeric binder. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Thus, it would have been obvious to one of ordinary skill in the art to modify the injection composition of Francois in view of the teaching of Ramstack, because Ramstack teaches the use of polymeric binder to obtain an injectable formulation having advantageous results over the conventional compositions, including a biodegradable system that prevents the loss of dose during treatment, microparticles free from

halogenated hydrocarbon residues, and the ability to program release to give faster or slower rates of drug release as needed (page 13, 2nd paragraph).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan T. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 6:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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